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14. ABSTRACT

The major goals and aims of this study are to investigate whether differences in cognitive outcome are related to mechanism of injury as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether MR variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

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INTRODUCTION

Aims and goals of the current project are to examine whether differences in neuropsychological outcome are related to mechanism of brain injury (blast versus blunt force) as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether imaging variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

BODY

Year 4: We have made considerable strides toward our stated goals as outlined in our Statement of Work. Our laboratory continues to grow at an exponential rate as we have expanded our collaborations and added key personnel, including a new UCSD/SDSU Joint-Doctoral Clinical Program graduate student, as well as a post-doctoral researcher. This year, we presented 6 studies at the International Neuropsychological Society meeting (Seattle, WA) and 1 study at the Associated Sleep Societies (Minneapolis, MN); the full abstracts for these 7 studies from 2014 are provided in the *Reportable Outcomes* section. We now have 4 studies stemming from these data published, while we have 3 manuscripts currently under review (citations for these 7 studies are provided in the "Manuscripts Published or In Press" and "Manuscripts Under Review" sections under *Reportable Outcomes* section*).*

During this fourth year of our DoD study, we have recruited and tested roughly 32 participants who represent either combat controls or patients who have sustained mild to moderate TBI. There are an additional 111 participants that were screened, but not included given that they did not meet inclusion criteria (e.g., were excluded from participating). We have conducted approximately 420 phone screens, of potential subjects throughout the course of the study. To date, we have enrolled a total of 89 subjects. Our recruitment rate is typically about 1-2 subjects per month. Our attrition rate is close to 0; our study subjects are informed in advance about the duration of the study, so they almost always complete both the cognitive assessment and neuroimaging sessions. After scanning, data is immediately pre-processed and prepared for analysis by skilled staff with expertise in imaging processing and analysis techniques. Fidelity checks of the data collected are thus evaluated as it is collected given that processing occurs within a day or two of data collection. Ongoing recruitment of patients and collection of relevant neuropsychological and behavioral outcome data occurs in tandem with neuroimaging (collected within one week of scanning, after obtaining appropriate consents). In addition, due to unanticipated slowed recruitment over the past year (e.g., we have experienced considerable challenges recruiting appropriate normal control participants that meet our inclusion criteria), we requested and were approved for a one-year no-cost extension (approved 10/21/2014). In order to fulfill our Statement of Work aims and to increase sample sizes (particularly with respect to rounding out our normal control sample to assist in group comparisons of the neuroimaging and other data) we have taken the following steps regarding recruitment: (1) We have amended our "control" recruitment flyer, as our old control flyers featured verbiage that may have been unclear with respect to our interest in control/non-TBI veterans; our old flyers were also displayed/concentrated in VA hospital locations where otherwise "healthy" veterans might not frequent, (2) We have also better utilized word-of-mouth referral with our current TBI and control participants by asking them to share our study information with veteran friends who may qualify, emphasizing that a history of TBI is not necessary for participation, (3) We continue to give talks to various VA clinicians, and we are now obtaining referrals through other research study mechanisms at the VASDHS (e.g., OEF/OIF/OND health intake study). Upkeep of regulatory approvals has also been necessary during this timeframe. Per our SOW, preliminary data analyses have been well underway over this past year.

Below is a summary of findings from the past year:

<u>6 studies at the International Neuropsychological Society meeting (Seattle, WA), full abstracts provided in *Appendices* :</u>

When examining the relationships among the cognitive effects of mTBI, PTSD symptom severity, and brain structure, results demonstrated that gray matter thickness was associated with PTSD symptom severity but not cognition, whereas white matter anisotropy was associated with cognition, but not PTSD symptom severity, suggesting dissociable neurobiologic substrates for the cognitive and psychological sequelae following mTBI (Sorg et al., 2014).

mTBI patients with poor effort endorse significantly greater psychiatric symptoms compared to those with optimal effort, although DTI indices reveal that WM integrity in those with poor effort is intermediate to those mTBI with intact vs. reduced cognition (Clark et al., 2014)

When compared to normal controls, mTBI veterans are more likely to report alcohol-related problems; younger and less-educated mTBI veterans appear to be at a higher risk of alcohol abuse. Alcohol abuse among mTBI veterans is associated with elevated psychiatric symptoms and slower visuomotor processing speed (Hanson et al., 2014).

When comparing mmTBI veterans with demographically-matched control veterans on measures of working memory (WM) and executive function (EF), we found that a subset of mmTBI veterans with poor WM/EF show a retrieval deficit, which is marked by reduced recall ability relative to recognition (Matevosyan et al., 2014).

When examining the relationship between coping style, executive function, and mood in veterans with mild-to-moderate TBI (mmTBI), we found that reduced executive function was strongly associated with greater usage of maladaptive avoidance coping; use of avoidance coping could not be explained by mood, PTSD symptoms, or effort (Kim et al., 2014).

Among middle- to older-age Veterans presenting with cognitive difficulties, those with an incidentally discovered history of TBI tended to be younger, potentially suggesting that TBI could influence the age at which cognitive difficulties emerge (Nation et al., 2014).

1 study at the Associated Sleep Societies (Minneapolis, MN), full abstract provided in *Appendices*:

Veterans with mTBI exhibit increased levels of sleep disturbance relative to Veterans who have not experienced mTBI. Poor sleep also appears to be associated with greater neuropsychiatric impairment in these individuals. Future research should attempt to examine the causal relationships between mTBI, sleep disturbance, and neuropsychiatric functioning in Veterans with mTBI (Orff et al., 2014).

Please find our most recent publication citation in *Reportable Outcomes* and *References*, and see the description below for a summary:

Schiehser et al., 2014a:

Traumatic brain injuries (TBI) are frequently accompanied by postconcussive symptoms (PCS) including but not limited to, fatigue, headache, dizziness, irritability, insomnia, mood disturbances, and cognitive symptoms that can persist in the months or years following the injury. With respect to these injuries, studies have found that long-term outcomes such as quality of life (QoL) are worse for individuals with TBI than for those without history of TBI. This study sought to assess the relationship between PCS and QoL in veterans with mild-to-moderate TBI (mmTBI). We found that perceived QoL was significantly worse in mmTBI veterans than in control veterans; in the mmTBI group, QoL was predominantly associated with affective symptoms, while moderate to strong correlations were found across all QoL areas for fatigue and depression. Further analyses revealed that depression and fatigue were the best predictors of Psychological, Social, and Environmental QoL, while sleep difficulty best predicted Physical QoL in mmTBI veterans. These findings therefore underscore the importance of examining *specific* symptoms as they relate to post-acute TBI QoL and provide guidance for treatment and intervention studies.

All tasks listed above have been completed by the following personnel (Dr. Delano-Wood, Russell Kim, Elisa Lanni, and Norman Luc). Elisa Lanni and Russell Kim have actively recruited and enrolled participants. They also assist Dr. Delano-Wood in imaging data collection, processing, and analysis. Neuropsychological testing takes place within the Neuropsychology Unit at the VA San Diego as part of clinical care for each patient. Appropriate releases are obtained for access to those data. For any individual who was not tested clinically, we conduct a 2 hour neuropsychological battery of cognitive tests. Assessment has been coordinated by Dr. Delano-Wood, Elisa Lanni, and Russell Kim. IRB continuing review has been spearheaded by Dr. Delano-Wood and Russell Kim. Finally, Elisa Lanni has coordinated the genetic testing (buccal swabbing) for the project.

KEY RESEARCH ACCOMPLISHMENTS

Citations for all key research accomplishments stated below are provided in *Appendices*:

- When examining the relationships among the cognitive effects of mTBI, PTSD symptom severity, and brain structure, results demonstrated that gray matter thickness was associated with PTSD symptom severity but not cognition, whereas white matter anisotropy was associated with cognition, but not PTSD symptom severity. These findings suggest dissociable neurobiologic substrates for the cognitive and psychological sequelae following mTBI (Sorg et al., 2014).

- mTBI patients with poor effort endorse significantly greater psychiatric symptoms compared to those with optimal effort; DTI indices reveal that WM integrity in those with poor effort is intermediate between those TBI with intact vs. reduced cognition. Findings suggest mTBI participants with poor effort may represent a heterogeneous group composed of those with and without WM abnormalities (Clark et al., 2014).

- When compared to normal controls, mTBI veterans are more likely to report alcohol-related problems; younger and less-educated mTBI veterans appear to be at a higher risk of alcohol abuse. Alcohol abuse among mTBI veterans is associated with elevated psychiatric symptoms and slower visuomotor processing speed. Taken together, these results emphasize the importance of assessing for and treating problematic alcohol use among veterans with history of neurotrauma (Hanson et al., 2014).

- When comparing mmTBI veterans with demographically-matched control veterans on measures of working memory (WM) and executive function (EF), we found that a subset of mmTBI veterans with poor WM/EF show a retrieval deficit, which is marked by reduced recall ability relative to recognition. As greater retrieval demands are required for semantic cueing compared to recognition, our results are consistent with a severe retrieval deficit in this particular subgroup. These findings highlight the role of WM/EF in retrieval of information and have implications for targeted assessment and cognitive interventions for specific mmTBI subgroups (Matevosyan et al., 2014).

- When examining the relationship between coping style, executive function, and mood in veterans with mild-to-moderate TBI (mmTBI), we found that reduced executive function was strongly associated with greater usage of maladaptive avoidance coping; use of avoidance coping could not be explained by mood, PTSD symptoms, or effort. These findings suggest that proper assessment and targeted cognitive interventions that focus on executive dysfunction may improve coping and long-term outcomes in this population (Kim et al., 2014).

- Among middle- to older-age Veterans presenting with cognitive difficulties, those with an incidentally discovered history of TBI tended to be younger, potentially suggesting that TBI could influence the age at which cognitive difficulties emerge. Those with a history of TBI were also more likely to have histories of mood and anxiety disorders, suggesting psychiatric factors may play a role in the interaction between cognitive aging and TBI (Nation et al., 2014).

- mTBI veterans report more sleep disturbance than control veterans; this sleep disturbance appears to be associated with greater neuropsychiatric impairment, suggesting the need for future research to examine the causal relationships between mTBI, sleep disturbance, and neuropsychiatric functioning in mTBI veterans (Orff et al., 2014).

- When assessing the relationship between PCS and QoL in mmTBI veterans versus control veterans, we found that mmTBI endorsed significantly worse QoL, and that in this group, depression and fatigue were the best predictors of Psychological, Social, and Environmental QoL, while sleep difficulty best predicted Physical QoL. These findings suggest the importance of examining *specific* symptoms of PCS as they relate to QoL and provide guidance for treatment and intervention studies (Schiehser et al., 2014).

REPORTABLE OUTCOMES

We have the following manuscripts and abstracts. The following studies were completed with joint funding from the VA and DoD.

6 Abstracts presented at the International Neuropsychological Society, Seattle, WA, February 2014:

Cognitive and Psychiatric Dissociations between Fractional Anisotropy and Cortical Thickness in Veterans with Mild TBI: (Scott Sorg, Mark W. Bondi , Dawn M. Schiehser, Norman Luc, Amy J. Jak, Alexandra Clark, Karen L. Hanson, James Lohr, Lisa Delano-Wood):
Objective: Studies using diffusion tensor imaging (DTI) have shown lower white matter integrity in veterans with history of mild TBI (mTBI). However, the effect of mTBI on gray matter regions remains understudied in this population. Thus, in a sample of veterans with mTBI, we investigated the relationships among the cognitive effects of mTBI, PTSD symptom severity, and brain structure in terms of gray matter measured via cortical thickness (CT) and white matter integrity measured via fractional anisotropy (FA). *Participants and Methods:* Thirty-eight mild TBI and 17 normal control (NC) veteran participants completed neuropsychological and psychiatric testing (e.g., PTSD Check List) with adequate effort, and underwent MRI scanning an average of 4 years following their TBI event(s). Mean CT measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interest.
Results: Adjusting for age, education, depression, and PTSD symptoms, mTBI participants performed worse than NCs on a memory composite and a test of psychomotor processing speed (p's<.05). CT did not differ between the mTBI and NC groups or correlate with cognitive test scores (p's>.05). Thinner left orbitofrontal CT was associated with higher PCL scores (p<.05). FA was lower in the TBI group than NCs in the left cingulum bundle (p<.05) and genu of the corpus callosum (p<.05). FA correlated with processing speed in seven tracts including the left cingulum (r=.38, p<.05) and genu (r=.50, p<.01). FA did not correlate with PCL scores (p>.05). Left cingulum bundle FA correlated with CT in the left middle frontal (r=.31, p<.05) and orbitofrontal cortices (r=.38, p<.01). *Conclusions:* Results demonstrated that gray matter thickness was associated with PTSD symptom severity but not cognition, whereas white matter anisotropy was associated with cognition but not PTSD symptom severity, suggesting dissociable neurobiologic substrates for the cognitive and psychological sequelae following mTBI.

Poor Effort is Associated with Increased Reporting of Injury Characteristics and Postconcussive Symptomatology but not Structural Brain Changes: A Multidisciplinary Study of OEF/OIF Veterans with History of Mild TBI. Alexandra L. Clark, Scott Sorg, Mark W. Bondi, Norman Luc, Dawn Schiehser, Karen Hanson, Dean C. Delis, Lawrence Frank, Amy J. Jak, James Lohr, & Lisa Delano-Wood **Background:** Studies investigating the role of effort in OEF/OIF Veterans with history of mild TBI (mTBI) have generally shown that poor effort is strongly associated with inflation on symptom rating scales, increased rates of clinical diagnoses, and decreased neurocognitive test performance. However, whether there are neurobiological abnormalities that underlie this pattern of increased symptom endorsement and clinical presentation in those who fail effort measures has not been studied. Therefore, the current study sought to explore the relationship between effort, symptom reporting, and structural brain changes (Freesurfer-derived values of cortical thickness and indices of white matter integrity using DTI) in OEF/OIF veterans with history of mTBI. **Method:** Ninety-seven (83M/14F) OEF/OIF Veterans (mean age = 31; mean time since injury = 2.3 years) underwent neuropsychological assessment and 3T MRI scanning. Participants were divided into those with history of mTBI who passed effort measures (mTBI-Pass: n = 52), those with mTBI who failed effort measures (mTBI-Fail: n = 16), and military combat controls (NC: n = 28) with no history of mTBI. Poor effort was defined by failure on the Test of Memory Malingering (TOMM) (Trial 1 score < 45) or CVLT Forced Choice Recognition (total score < 15)..Mean cortical thickness measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interests. **Results:** Collapsed across effort, when compared to the NCs, the overall mTBI group showed significantly elevated scores on measures of PTSD (p = .001), depression (p = .01), and anxiety (*p* = .015). Within the mTBI group, in comparison to the mTBI-Pass subgroup, the mTBI-Fail subgroup reported less time since their most recent TBI (p = .03) and higher levels on all psychiatric measures (PTSD, depression, and anxiety; all *p*-values < .002). Additionally, the mTBI-Fail subgroup reported significantly more severe injury characteristics (LOC, AOC, PTA; all *p*-values < .05) and increased postconcussive severity (*p* < .015) in the context of reduced performance across multiple cognitive domains measured (all p-values < .05). However, although the overall mTBI group showed greater white matter and cortical thickness abnormalities when compared to NCs, there were no significant differences between the mTBI-Pass and mTBI-Fail groups on any of the imaging indices examined. **Conclusions:** Despite considerably elevated subjective complaints, injury severity reporting, and symptom endorsement in those with mTBI with low vs. high effort results of this study show that, in our cohort of mTBI veterans with poor effort, there are no objective gray or white matter differences –above and beyond those attributable to mTBI—that might explain this pattern of exaggerated injury and symptom reporting. Future research focusing on symptom attribution and illness perception may aid in understanding more about the relationship between reduced effort and increased symptom endorsement patterns following neurotrauma in this vulnerable population.

Alcohol Misuse is Associated with Increased Psychiatric Symptomatology and Reduced Processing Speed in Veterans with Mild Traumatic Brain Injury. (Karen L. Hanson, Ph.D., Dawn M. Schiehser, Ph.D., Elizabeth Twamley, Ph.D., Amy J. Jak, Ph.D., Alexandra L. Clark, B.A. , James B. Lohr, Ph.D. Dean C. Delis, Ph.D. & Lisa Delano-Wood, Ph.D.[)] *Introduction:* Given that little is known about the role of alcohol misuse in the cognitive and psychiatric outcomes among veterans with mild traumatic brain injury (mTBI), we aimed to: (1) characterize how veterans with mTBI differ from military combat controls on measures of alcohol misuse, psychiatric symptomatology, and cognition; (2) determine the risk factors for problematic alcohol use among veterans with mTBI; and (3) examine whether problematic alcohol use is associated with increased psychiatric symptoms and reduced cognition among veterans with mTBI. *Methods:* 77 veterans (n=48 with mTBI history; n=29 veteran combat normal controls [NCs]; mean age = 31.9; 14% women) completed an assessment of problematic alcohol use (Alcohol Use Disorders Identification Test: AUDIT), psychiatric symptoms, and neuropsychological (NP) functioning. Participants who reported current (within 30 days) alcohol or substance dependence (DSM-IV criteria) or a positive toxicology screen taken on the day of testing were excluded from the study. Only participants who demonstrated optimal effort (64/77) upon testing were included in the cognitive analyses. *Results:* Compared to NCs, there was a trend revealing that the mTBI group was more likely to score above the AUDIT cut-off score of 8 (*p*=.066). Within the mTBI group, higher AUDIT scores correlated with younger age at testing (*r*= -.45, *p*=.001) and lower education (*r*=-.30, *p*=.007), as well as the following injury characteristic variables: younger age at last TBI (rho=-.38, p=.01), shorter (?) post-traumatic amnesia duration (rho=-.60, p=.001), and increased blast-related quaternary effects (*rho*=.45, p=.019). When compared to the mTBI group with low AUDIT scores, the mTBI group scoring above the AUDIT cutoff reported higher levels of depression(*p*=.005) and anxiety (*p*=.02), and increased neurobehavioral symptoms (*p*=.026)), but there were no differences on PTSD symptoms p = .11). Finally, higher AUDIT scores were associated with slower visuomotor processing speed (*p* = .02) but not other NP domains. *Conclusion:* Findings suggest that (1) compared to NCs, mTBI veterans are more likely to report alcohol-related problems, (2) younger and less educated mTBI veterans appear to be at higher risk for alcohol abuse and (3) alcohol abuse among mTBI veterans is associated with elevated psychiatric symptoms and slower visuomotor processing speed. These results emphasize the importance of assessing for and treating problematic alcohol use among veterans with history of neurotrauma.

Memory Deficits Differ by Working Memory Performance in Mild to Moderate Traumatic Brain Injury (Matevosyan, A., Delano-Wood, L.M., Alhassoon, O., Filoteo, J.V., Lanni, E.B., Kim, R., Hanson, K.L, & Schiehser, D.M.)
Objective: Memory problems are common in the context of mild to moderate traumatic brain injury (mmTBI); however, the nature of memory deficits in this population is not entirely clear. Given the relationship between working memory/executive function (WM/EF) and organization of information for adequate retrieval, we hypothesized that individuals with mmTBI who demonstrate poor WM/EF will present with a retrieval deficit, which is characterized by better recognition or cued recall as compared to free recall.
Participants and Methods: Veterans with a history of mmTBI (n=46; mean years since injury=6.6) and 17 demographically-matched veteran normal controls (VNC) with optimal effort were administered the California Verbal Learning Test (CVLT-II) and the Wechsler Adult Intelligence ScaleDigit Span Backwards (DSB) test. The mmTBI group was divided into low WM/EF (LDSB) and high WM/EF (HDSB) using a median split of the DSB scores (raw≤8.5).
Results: A One-Way MANOVA revealed significant differences between LDSB, HDSB, and VNC on measures of total (Trials 1-5), free, and cued recall (all p's ≤ .01), but not recognition (p=.08). Post-hoc analyses revealed that LDSB participants performed significantly worse on total, free, and cued recall compared to VNC, while they performed significantly worse on total and free recall compared to the HDSB group (all p's<.02); no differences in recognition were found between either groups. No significant differences were found on any of the memory measures between HDSB and VNC (all p's>.25).
Conclusions: Results indicate that a subset of mmTBI individuals with poor WM/EF show a retrieval deficit, which is marked by reduced recall relative to recognition. As greater retrieval demands are required for semantic cueing compared to recognition, our results are consistent with a severe retrieval deficit in this particular subgroup. These findings highlight the role of WM/EF in retrieval of information and have implications for targeted assessment and cognitive interventions for specific mmTBI subgroups.

Executive Dysfunction is Associated with Avoidance Coping Style in Veterans with Mild to Moderate Traumatic Brain Injury. Kim, R., Delano-Wood, L., Bondi, M.W., Hanson, K.L., Matevosyan, A., Lanni, E.B., Luc, N., & Schiehser, D.M. Objective: Preliminary evidence suggests that individuals with traumatic brain injury (TBI) may utilize maladaptive coping styles, such as avoidance or emotional reaction (e.g., self-blame), more than functional task-oriented coping styles. Since executive dysfunction is frequently observed in veterans with history of TBI, we sought to investigate the relationship between coping style and performance on executive tasks in this population. Participants and Methods: Participants were veterans (n = 20) with a history of mild to moderate TBI (6.9 mean years since injury) and veteran combat normal controls (NCs: n = 18) without a history of TBI. All participants were administered measures of coping (Coping Inventory for Stressful Situations), executive function (Color-Word Interference Test; CWIT), depression (Beck Depression Inventory-II), anxiety (Beck Anxiety Inventory), and Post-traumatic Stress Disorder (PTSD) symptoms (PTSD Checklist-Military Version). Results: Controlling for age, depression, anxiety, and PTSD, the TBI group reported significantly greater usage of Avoidance coping when compared to NCs; groups did not differ in their use of Task or

Emotional coping (all *p*'s > .05). In the mTBI group, Avoidance coping was significantly associated with worse CWIT Inhibition/Switching (*p* = .03), but was not related to depression, anxiety, or PTSD (all *p*'s > .56). Both Task and Emotional coping were associated with mood (all *p*'s < .01), but were unrelated to executive function. Conclusions: Taken together, our findings demonstrate that veterans with history of mild to moderate TBI endorsed greater avoidance coping compared to combat controls with no history of neurotrauma. In TBI veterans, greater use of avoidance coping was associated with poorer executive function. Additionally, task and emotional coping was related to increased psychiatric symptomatology (depression, anxiety, and PTSD). These findings underscore the impact of reduced executive function on maladaptive coping, and they suggest that proper assessment and targeted cognitive and psychological interventions may improve long-term outcomes in this vulnerable population.

Correlates of TBI History in Aging Veterans Presenting with Cognitive Difficulties: A Clinical Case Series: (Nation, D.A., Abuyo, T., Delano-Wood, L., Jak, A.J., Bondi, M.W. Objective) We sought to investigate the relationship between cognitive aging and history of traumatic brain injury (TBI) among aging veterans in order to further our understanding of the interaction between TBI and age-related cognitive disorders. *Methods:* A case series of 104 Veterans (age mean=70.5, range=46-89; 94.2% male) referred for neuropsychological evaluation of cognitive difficulties (self- or informant-report) were compared on demographics, cognition, and psychiatric history based on whether there was history of TBI (n=54) or not (n=50). No participants were referred because of a known TBI, but history of TBI was assessed during clinical interview and chart review. Analyses were performed across the entire sample and after stratification by clinical diagnosis [normal cognition, Cognitive Disorder, or Dementia]. The main effects of TBI history and the interaction of TBI history with clinical diagnoses were evaluated by ANOVA. Chi-square analyses compared rates of anxiety, depression, PTSD, and alcohol/substance abuse history. *Results:* There was a main effect of TBI history on age at presentation, such that Veterans with a history of TBI were younger than those without a history of TBI (p=.001). Veterans with a history of TBI were also more likely to have a history of anxiety (p=.01) and PTSD (p=.026), but were no more likely to exhibit depression or alcohol/substance abuse. There were no differences in dementia rating scale scores. *Conclusions:* Among middle- to older-age Veterans presenting with cognitive difficulties, those with an incidentally discovered history of TBI tended to be younger, potentially suggesting that TBI could influence the age at which cognitive difficulties emerge. Those with a history of TBI were also more likely to have histories of mood and anxiety disorders, suggesting psychiatric factors may play a role in the interaction between cognitive aging and TBI.

1 Abstract presented at the Annual Meeting of the Associated Professional Sleep Societies, Minneapolis, MN, May 2014:

Sleep Disturbance and Neuropsychiatric Functioning in Veterans with Mild to Moderate Traumatic Brain Injury (mTBI) Compared with non-mTBI Veterans
(H. Orff, D. Schiehser, E. Twamley, A. Jak, S. Drummond, L. Delano-Wood).
Background: Many Veterans of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) experience post-concussive symptoms associated with a history of mild to moderate traumatic brain injury (mTBI). Sleep complaints are highly prevalent in post-mTBI Veterans, however the degree and impact of impairment, relative to Veterans who have not experienced mTBI, is largely unknown.
Methods: Veterans enrolled for studies of mTBI at the VA San Diego Healthcare System received a comprehensive screening of sleep (Pittsburgh Sleep Quality Inventory-PSQI; Insomnia Severity Index-ISI; Epworth Sleepiness Scale-ESS; Multidimensional Fatigue Inventory-MFI), psychiatric symptoms, post-concussive symptoms, alcohol/substance use, and

quality of life. Results were compared using independent samples t-tests and bivariate correlations to explore differences between Veterans with and without mTBI.
Results: 21 Veterans with a history of mTBI (18M; age=32 yrs; education=14 yrs) and 17 Veterans with no history of mTBI (14M; [3 with combat experience]; age=34 yrs; mean=14 yrs) were studied. Compared to the non-mTBI group, the mTBI group exhibited significantly greater sleep disturbance (PSQI; p=.004), more insomnia symptoms (ISI; p=.018), more daytime sleepiness (ESS; p=.002), and higher levels of fatigue (MFI; p<.001). The mTBI group also exhibited significantly elevated depressive, anxious, PTSD-related, and post-concussive/neurobehavioral symptoms (all ps<.001), however, the groups did not differ on alcohol/substance abuse or quality of life measures. PSQI Global scores were significantly correlated with lower quality of life and higher PTSD symptom severity in both groups. Additionally, PSQI Global scores were correlated with higher levels of post-concussive symptoms, anxiety symptom severity, and fatigue severity in mTBI Veterans.
Conclusion: Veterans with mTBI exhibit increased levels of sleep disturbance relative to Veterans who have not experienced mTBI. Poor sleep also appears to be associated with greater neuropsychiatric impairment in these individuals. Future research should attempt to examine the causal relationships between mTBI, sleep disturbance, and neuropsychiatric functioning in Veterans with mTBI.

<u>Manuscripts Published or In Press:</u>

Schiehser, D.M., **Delano-Wood, L.,** Jak, A.J., Matthews, S., Simmons, S., Jacobson, M.J., Filoteo, J.V., Bondi, M.W., Orff, H., & Liu, L. (2014a). Validation of the Modified Fatigue Impact Scale in Mild to Moderate Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation[epub ahead of print].*

Schiehser D.M., Twamley E.W., Liu L., Matevosyan A., Filoteo J.V, Jak A.J., Orff H.J., Hanson K., & Delano-Wood L. (2014b). The Relationship Between Postconcussive Symptoms and Quality of Life in Veterans with Mild to Moderate Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation[epub ahed of print].*

Sorg, S.F., **Delano-Wood, L.,** Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W. (2014). White matter integrity in veterans with mild traumatic brain injury: Associations with executive function and loss of consciousness. *Journal of Head Trauma Rehabilitation, 29*(1), *21-32.*

Schiehser, D.M., Delis, D.C., Filoteo, J.V., Delano-Wood, L., Han, S.D., Jak, A.J., Drake, A.I., & Bondi, M.W. (2011). Are self-reported symptoms of executive dysfunction associated with objective executive function performance following mild to moderate traumatic brain injury? *J Clin Exp Neuropsychol, 33(6), 704-14.*

<u>Manuscripts Under Review:</u>

Clark, A.L., Sorg, S.F., Schiehser, D.M., Bigler, E., Bondi, M.W., Luc, N., Kim, R., Jacobson, M.W., Jak, A.J., & Delano-Wood, L. (under review). White Matter Associations with Performance Validity Testing in Veterans with Mild Traumatic Brain Injury (mTBI): The Utility of Biomarkers in Complicated Assessment. *Journal of Head Trauma Rehabilitation.*

Jak, A.J., Gregory, A., Orff, H.J., Colon, C., Steele, N., Schiehser, D., Delano-Wood, L., & Twamley, E.W. (under review). Neuropsychological Presentation of OEF/OIF Veterans with a History of Mild to Moderate TBI. *Journal of Clinical and Experimental Neuropsychology*.

Sorg, S.F., Schiehser, D.M., Bondi, M.W., Luc, N., Clark, A.L., Jacobson, M.W., & Delano-Wood, L. (under review). Does TBI-Related White Matter Microstructural Compromise in Military Veterans Contribute to Post-Traumatic Stress Disorder Symptoms? *Journal of Neurotrauma.*

Presentations:

As part of a VA-sponsored National Webinar, Dr. Dawn Schiehser presented "Diagnosis, Mechanism, and Management of Fatigue in Mild Traumatic Brain Injury" (June 24, 2014). The web URL for this presentation is provided below in *References.*

CONCLUSION

We continue to make considerable progress toward our stated goals as outlined in our Introduction above. Given greater collaborations with other VA TBI investigators, our laboratory has grown considerably and productivity has increased significantly. Collectively, my laboratory has completed several studies, 4 that our now published or in press, and another 3 that are currently under review in peer-reviewed journals. Recruitment continues at a solid pace, with another 32 participants scanned and tested in this past year. We expect to be especially productive this year and next, especially in regard to increased recruitment efforts, as we continue to grow our lab while also rounding out our data collection so that we can then embark upon large-scale studies to test many of the hypotheses set forth in the original proposal.

REFERENCES

Schiehser, D.M., **Delano-Wood, L.,** Jak, A.J., Matthews, S., Simmons, S., Jacobson, M.J., Filoteo, J.V., Bondi, M.W., Orff, H., & Liu, L. (2014a). Validation of the Modified Fatigue Impact Scale in Mild to Moderate Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation[epub ahead of print]*.

Schiehser D.M., Twamley E.W., Liu L., Matevosyan A., Filoteo J.V, Jak A.J., Orff H.J., Hanson K., & Delano-Wood L. (2014b). The Relationship Between Postconcussive Symptoms and Quality of Life in Veterans with Mild to Moderate Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation[epub ahed of print]*.

Schiehser, D.M. (2014, June 24). Diagnosis, Mechanism, and Management of Fatigue in Mild Traumatic Brain Injury. Retrieved from http://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=853

APPENDICES

We list below publications and abstracts that were submitted since the start of the study:

The following are abstracts for 3 of the most recently published manuscripts:

Validation of the Modified Fatigue Impact Scale in Mild to Moderate Traumatic Brain Injury: (Dawn M. Schiehser, Lisa Delano-Wood, et al., In press, Journal of Head Trauma Rehabilitation). *Objective*: To evaluate the validity of the Modified Fatigue Impact Scale (MFIS) in a traumatic brain injury (TBI) military population. *Methods:* Participants were OEF/OIF/Gulf War veterans with a history of mild to moderate TBI (*N* = 106). Factor structure, internal consistency, convergent validity, sensitivity, and specificity of the MFIS were examined. The relationship between sample characteristics and the MFIS scores was also evaluated.*Results*: Principal Component Analysis identified two viable MFIS factors: a Cognitive subscale and a Physical subscale. Item analysis revealed high internal consistency of the MFIS Total scale and subscale items. Strong convergent validity of the MFIS scales was established with two Beck Depression Inventory (BDI-II) fatigue items. ROC analysis revealed good to excellent accuracy of the MFIS in classifying fatigued versus non-fatigued individuals. Furthermore, higher levels of overall and physical fatigue, but not cognitive fatigue, were associated with the presence of post-traumatic amnesia at injury. *Conclusion*: The MFIS is a valid multidimensional measure that can be used to evaluate cognitive and physical fatigue in individuals with mild to moderate TBI. Differences in the relationships between TBI characteristics and fatigue subtypes underscore the utility of a multidimensional fatigue scale in this population.

The Relationship between Post-Concussive Symptoms and Quality of Life in Veterans with Mild to Moderate TBI: (Schiehser D.M., Twamley E.W., Liu L., Matevosyan A., Filoteo J.V, Jak A.J., Orff H.J., Hanson K., & Delano-Wood L.) Objective: To assess the relationship between Quality of Life (QoL) and specific neurobehavioral symptoms in military veterans with mild to moderate postacute (>6 months) traumatic brain injury (TBI). *Methods:* Participants were 61 Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/Persian Gulf veterans with mild or moderate TBI and 21 demographically-matched military control participants. All participants were administered self-report measures of quality of life (QoL; World Health Organization Quality of Life -BREF) and neurobehavioral symptom severity (Neurobehavioral Symptom Inventory). *Results*: Veterans with mild to moderate TBI reported worse QoL compared to the control group. Affective symptoms best predicted Physical, Social, and Environmental QoL, with fatigue emerging as the only significant predictor. Depression, headache, sleep difficulty, attention problems, appetite changes, and irritability were significantly associated with specific areas of QoL.*Conclusion*: Specific neurobehavioral symptoms are associated with different self-reported ratings of QoL in veterans with postacute mild to moderate TBI. Affective symptoms, and most predominantly fatigue, appear to be the most relevant neurobehavioral symptoms predicting postacute QoL. Our results have the potential to optimize targeted treatments to improve QoL in this vulnerable population.

White Matter Integrity in Veterans Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness: (Sorg, S.F., Delano-Wood, L**.**, Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W). A sample of carefully selected participants who displayed adequate effort, we have been able to show executive impairment in a subset of OEF/OIF veterans who have sustained mild to moderate TBI. These findings showed that, although there were no significant overall group differences between control and mTBI participants on DTI measures, a subgroup of mTBI participants with executive dysfunction demonstrated reduced white matter integrity of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without executive dysfunction. Interestingly, participants with TBI with loss of consciousness (LOC) were more likely to evidenced executive function difficulties and disrupted ventral prefrontal white matter integrity when compared to either TBI participants without LOC or control participants. Findings suggest that altered white matter integrity contributes to reduced executive functioning in subgroups of veterans with history of mTBI and LOC may be a risk factor for reduced executive function as well as associated changes to ventral prefrontal white matter.

The following are 3 abstracts presented at the International Neuropsychological Society, Honolulu, HI, 2013:

Fornix Integrity is Related to Cognition but not Postconcussive Symptoms in Chronic Military Traumatic Brain Injury: A Quantitative Tractography Study: Delano-Wood, L., Sorg, S.F., Luc, N.K., Schiehser, D.M., Lanni, E.B., Jacobson, M.W., Nation, D.A., Jak, A.J., Hanson, K.L., Frank, L.R., Meloy, M.J., Delis, D.C., Lohr, J.B., & Bondi, M.W.
Objective: White matter (WM) changes have been reported in mild TBI, although few diffusion tensor imaging (DTI) tractography studies of military personnel exist in the literature. This study investigated the fornix, a WM limbic structure that is particularly vulnerable to TBI-related diffuse axonal injury. Given this structure's connectivity and cholinergic input to the medial temporal lobe (MTL), we investigated associations between fornix microstructural integrity and cognition in both blast-related and mechanical blunt force mTBI. *Participants and Methods:* Seventy-three military veterans (mTBI: n = 53; NC: n = 20) were administered 3T DTI scans (61 directions) and a comprehensive neuropsychological evaluation. White matter tracking was employed by seeding ROIs in bilateral contiguous slices on a registered T1 image and mean DTI values were derived from individual fractional anisotropic (FA) and mean diffusivity (MD) maps. *Results:* The mTBI group performed significantly more poorly than NCs across several neuropsychological domains including attention/working memory, executive functioning, visual and verbal memory, and fine motor dexterity. Independent samples t-tests demonstrated that the mTBI group differed significantly from NCs on fornix FA (t = 3.00(71) $t = 3.00_{[df= 71]}$, $p = .004$) as well as fornix MD ($t = -2.10_{[df= 71]}$, $p = .038$), but not on fornix volume (p = .22). Moreover, fornix DT indices positively correlated with performance on attention/working memory, executive functioning, and fine motor dexterity. Finally, mTBI subgroup analysis of blast, blunt, and NCs subgroups significantly differed on fornix MD (F = 3.47(75) = .036), fornix AD (F = 4.25(75), = .018), and trend with fornix RD (F = 2.74(75) = .07).

Iowa Gambling Task Impairment is Associated with Executive Dysfunction in Veterans with Chronic Mild to Moderate Traumatic Brain Injury: (Luc, N.K., Nation, D.A., Sorg, S.F., Schiehser, D.M., Hanson-Bondi, K.L., Bondi M.W., Lanni, E., Jak, A.J., Matsevoyan, A., Kim, R., Jacobson, M., & Delano-Wood L). *Objective:* The Iowa Gambling Task (IGT) has been widely employed to examine risk-related decision-making performance across several clinical populations; however, few studies have investigated performance on this task in the context of traumatic brain injury (TBI). Given that decision-making likely plays an important role in long-term functional outcome following neurotrauma, the current study compared IGT performance between OEF/OIF veterans with a history of chronic mild to moderate TBI and normal control (NC) participants. We hypothesized that mTBI patients would demonstrate deficits in decision-making and that IGT performance would be related to other measures of executive functioning. *Participants and Methods:* Forty-seven demographically-matched participants (TBI: n=26; NC n=21; mean age = 32.7; mean months since TBI = 80.7) were administered a comprehensive neuropsychological battery which included a computerized version of the IGT. Participants were divided into impaired and unimpaired performance on IGT based on a T-score cutoff corresponding to > 1 standard deviation below the mean ($T \leq 39$). *Results:* TBI participants were significantly more likely to exhibit impairment on the IGT total score relative to the NC group (% Impaired: TBI = 20.7%; NC = 0%; $p = .02$). Repeated measures ANOVA indicated a significant group by block interaction ($p = .04$), whereby the TBI group performed significantly worse than NCs on block 4 ($p = .03$) and were more likely to exhibit impairment on 2 or more blocks (% Impaired: TBI = 19.2%; NC = 0%). Collapsed across group, IGT performance was negatively related to executive functioning (DKEFS Trails Switching [$r= -.36$, $p= .02$], WCST Perseverative Responses [$r= -.35$, $p=.02$], and Set Losses [r -.30, $p = .049$]). *Conclusions:* Findings indicate that mild to moderate military TBI is associated with subtle impairment in reward-related decision-making and suggest that the IGT may be a sensitive index of this aspect of executive dysfunction in military chronic TBI.

Processing Speed and Memory Deficits in Veterans with Mild to Moderate TBI: Associations with Anterior White Matter Integrity: Scott Sorg, Lisa Delano-Wood, Dawn M. Schiehser, Norman Luc, Elisa Lanni, Amy J. Jak, Karen L. Hanson, M. J. Meloy, Daniel A. Nation, Mark Jacobson, Lawrence R. Frank, James Lohr, Mark W. Bondi. *Objective:* High rates of mild to moderate traumatic brain injuries (TBI) are reported in veterans of the Iraq and Afghanistan wars. The long-term neuropsychological outcome of these injuries and their relationship with cerebral white matter microstructure is unclear. Using diffusion tensor imaging (DTI) tractography, this study investigated the effects of TBI on a sample of veterans in terms of cognition and white matter integrity. *Participants and Methods:* Thirty-eight veterans with TBI and 17 veteran normal control (NC) participants completed neuropsychological and psychiatric testing with adequate effort and underwent a DTI scan an average of 4 years following their TBI event(s). Fractional anisotropy (FA), a measure of white matter integrity, was extracted from 7 white matter tracts. *Results:* TBI participants had higher depression and PTSD scores than the control group and completed fewer years of education. Controlling for age, education, depression, and PTSD symptoms, ANCOVA revealed that TBI participants performed worse than NCs on a memory composite ($p=.02$, $\eta2=.11$) and on a test of psychomotor processing speed ($p=.02$, $\eta2=.11$), whereas the two groups did not differ on an executive function composite ($p=.37$, $\eta2=.02$) or on a measure of attention ($p=.56$, $\eta2=.01$). The TBI group evidenced lower FA in the left cingulum bundle ($p=.01$, $\eta2=.13$) and in the genu of the corpus callosum ($p=.03$, $\eta2=.09$). Partial correlations adjusting for age and education showed significant positive associations between psychomotor processing speed and FA in the left cingulum ($r=.38$, $p=.04$), genu ($r=.50$, $p<.01$) and body of the corpus callosum ($r=.52$, $p<.01$), and left posterior internal capsule ($r=.45$, $p=.01$). *Conclusions:* Results suggest that the cognitive consequences of TBI may be enduring in veterans, and may be associated with poorer performance in memory and processing speed. Findings further suggest that slowed processing speed may be a consequence of TBI-related damage to anterior white matter pathways.

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The Relationship Between Postconcussive Symptoms and Quality of Life in Veterans With Mild to Moderate Traumatic Brain Injury

Dawn M. Schiehser, PhD; Elizabeth W. Twamley, PhD; Lin Liu, PhD; Adelina Matevosyan, MA; J. Vincent Filoteo, PhD; Amy J. Jak, PhD; Henry J. Orff, PhD; Karen L. Hanson, PhD; Scott F. Sorg, PhD; Lisa Delano-Wood, PhD

Objective: To assess the relationship between postconcussive symptoms and quality of life (QOL) in Veterans with mild to moderate traumatic brain injury (TBI). **Methods:** Sixty-one Operation Enduring Freedom/Operation Iraqi Freedom/Persian Gulf War Veterans with a history of mild or moderate TBI, more than 6 months postinjury, and 21 demographically matched Veteran controls were administered self-report measures of QOL (World Health Organization Quality of Life–BREF) and postconcussive symptom severity (Neurobehavioral Symptom Inventory). **Results:** Perceived QOL was significantly worse in Veterans with mild-moderate TBI than in controls. In the TBI group, QOL was predominantly associated with affective symptoms, and moderate to strong correlations with fatigue and depression were evident across all QOL areas. Multivariate analyses revealed depression and fatigue to be the best predictors of Psychological, Social, and Environmental QOL, whereas sleep difficulty best predicted Physical QOL in mild-moderate TBI. **Conclusion:** Veterans with post–acute mild-moderate TBI evidence worse QOL than demographically matched Veteran controls. Affective symptoms, and specifically those of fatigue, depression, and sleep difficulty, appear to be the most relevant postconcussive symptoms predicting QOL in this population. These findings underscore the importance of examining specific symptoms as they relate to post–acute TBI QOL and provide guidance for treatment and intervention studies. **Key words:** *depression, fatigue, postconcussive symptoms, quality of life, sleep, traumatic brain injury*

APPROXIMATELY 1.7 million individuals sustain a traumatic brain injury (TBI) every year in the United States.[1] Traumatic brain injury is also a significant problem for military personnel, with TBI occurring in approximately 19% of recent surviving combat casualties.[2] The vast majority of brain injuries are classified as mild to moderate in severity and are frequently accompanied by postconcussive symptoms including, but not limited to, fatigue, headache, dizziness, irritability, insomnia, mood disturbances, and cognitive symptoms.[3,4] Although many of these symptoms often resolve within days or weeks following a mild to moderate TBI, symptoms can persist in the months or years following the injury.[4]

With the increased prevalence of diagnosed mild TBI[5] and unresolved postconcussive symptoms in US military personnel and Veterans, long-term outcomes, such as quality of life (QOL), have emerged as an important and needed area of research. Although definitions vary, QOL can be conceptualized as a person's perception of his or her physical, emotional, and social well-being. Specifically, the World Health Organization Quality of Life Group defined QOL as

> an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and

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in relation to his/her goals, expectations, standards and concerns. It is a broad ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment.[6(p1405)]

In general, individuals with a history of TBI report worse QOL than that reported by control groups (for a review, see Dijkers[7]), which can persist 10 years or more after the injury.[8,9] In a recent Swiss study, QOL was significantly worse in a post–acute mixed severity TBI group than in the group with preinjury levels as well as in demographically matched polytrauma patients,[10] suggesting that the brain injury rather than premorbid functioning or general (nonbrain injury) trauma plays a role in QOL. Generalization of these findings to a mild-moderate sample is limited, as the majority of these studies have used a large range of severity levels, severe TBI, and/or acute TBI samples. However, one study revealed similar findings of worse QOL in a general community sample of individuals with post–acute (>6 months) mild-moderate TBI than in controls.[11]

Research on the most pertinent postconcussive factors associated with QOL in mild to moderate post–acute TBI, and particularly in Veterans with TBI, is limited. The relationships between QOL and demographic or injury characteristics have been inconsistent,[7,12,13] rendering it unclear if age, education, gender, TBI severity, loss of consciousness (LOC), or posttraumatic amnesia (PTA) are related to QOL. Although one study demonstrated that a greater number of postconcussive symptoms was associated with worse QOL in mild TBI,[14] the specific relationships between types of postconcussive symptoms and QOL were not reported and remain largely unknown in this population. Several studies using mixed severity and/or civilian or non-US TBI samples have found a significant relationship between QOL and depression,[15–17] pain,[17] and fatigue.[18] However, it is difficult to compare these studies or draw conclusions regarding the relationship between postconcussive symptoms and QOL, as these studies varied with regard to sample characteristics as well as outcome measures, which were often limited to a few preselected symptoms. Findler and colleagues[11] explored the relationship between QOL and a comprehensive sampling of postconcussive symptoms in mild-moderate post–acute TBI, finding that cognitive, affective, and physical postconcussive symptoms were associated with all aspects of QOL; again, however, this study did not examine associations with specific symptoms or degree of symptomatology. As individual symptoms can overlap between designated domains (eg, fatigue can be a symptom of cognitive, affective, or physical symptom domain), examining specific symptoms is warranted. Furthermore, such an examination is necessary, as it can help determine which symptoms clinicians might prioritize for treatment and intervention strategies.

The purpose of this study was to (1) examine the differences between QOL in Veterans with and without mild to moderate post–acute (>6 months) TBI, (2) assess the relationship between postconcussive symptoms and QOL in mild to moderate TBI, and (3) explore the relative contribution of specific postconcussive symptoms to Physical, Psychological, Social, and Environmental QOL. We hypothesized that (1) Veterans with mild to moderate TBI would report significantly worse QOL than Veterans without a history of TBI; (2) postconcussive symptoms would be significantly associated with worse QOL in the TBI group, and (3) symptoms of depression, pain (headaches), and fatigue would be associated with all aspects of QOL.

METHODS

Participants

Table 1 provides demographic and injury characteristics of the TBI and control groups. Sixty-one Operation Enduring Freedom/Operation Iraqi Freedom ($n = 56$) and Persian Gulf ($n = 5$) Veterans with mild or moderate TBI and 21 Operation Enduring Freedom/Operation Iraqi Freedom ($n = 16$) and Persian Gulf ($n = 5$) Veterans without a history of TBI were recruited for this study. Traumatic brain injury was defined by the VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury as

a traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least *one* of the following: (1) any period of LOC; (2) any loss of memory for events immediately before or after the injury (PTA); (3) any alteration in mental state at the time of the injury (alteration of consciousness; AOC); or (4) neurological deficits that may or may not be transient.[19(p1)]

Fifty-four participants (88.5% of TBI sample) met criteria for *mild* TBI, defined by (*a*) an initial LOC of less than 30 minutes, (*b*) AOC up to 24 hours, and/or (*c*) PTA of less than 24 hours. Seven participants (11.5% of TBI sample) met criteria for *moderate* TBI, defined by (*a*) an initial LOC of greater than 30 minutes and less than 24 hours, (*b*) AOC greater than 24 hours, and/or (*c*) PTA greater than 24 hours but less than 7 days.[19(p2)]

As is common in retrospective studies of military personnel, medical records regarding length of LOC/AOC, Glasgow Coma Scale scores, and PTA are often unavailable and information is frequently obtained by patient self-report. No Glasgow Coma Scale scores were available for this study, and all information (LOC, PTA,

TABLE 1 *Demographic and injury severity characteristics*

	TBI patients ($n = 61$)	Veteran controls ($n = 21$)	P
Age, median; mean (SD), y	31; 32 (7.4)	31; 33 (8.9)	.619
Education, median; mean (SD), y	14; 14 (1.7)	13; 14 (2.2)	.234
Gender (male:female)	57:4	15:6	**.015**
Combat exposure (% yes)	72%	52%	.113
Most significant TBI sustained on deployment (% yes)	64%	...	...
Number of TBIs, median; mean (SD)	2.0; 2.4 (1.5)	...	...
Months since most significant TBI, median; mean (SD)	61; 69 (44)	...	...
Age at most significant TBI, median; mean (SD)	24; 27 (6.7)	...	...
Severity of most significant TBI		...	...
Mild	88%	...	...
Moderate	12%		
LOC/AOC during most significant TBI			
LOC	66%	...	...
AOC (no LOC)	34%		
PTA during most significant TBI			
Yes	46%	...	...
No	42%		
Unsure	12%		
Type of most significant TBI			
Blunt	66%	...	...
Blast/no secondary injury	16%		
Blast + secondary blunt injury	18%		

Abbreviations: AOC = alteration of consciousness during TBI event; LOC, loss of consciousness during TBI event; PTA, posttraumatic amnesia; TBI, traumatic brain injury.
Bold value indicates significance at *P* level.

combat exposure) was determined by participant self-report through the use of the Combat Exposure Scale[20] and a semi-structured clinician-administered interview that allowed for open-ended queries of responses that required elaboration. The single "most significant" or "worst" TBI was determined by participant report in conjunction with self-reported LOC and PTA durations (Table 1). Participants were also interviewed regarding the total number of self-reported lifetime TBI events, which were recorded if the incidents met aforementioned TBI criteria.

Exclusion criteria for this study included (1) any current (within 30 days) substance or alcohol abuse/dependence according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria; (2) a history of a neurological or metabolic disorder or disease known to affect the central nervous system (besides TBI for the TBI group); (3) a history of bipolar disorder, schizophrenia, or other psychotic disorders; and (4) a history of severe TBI defined by an initial LOC of greater than 24 hours and/or PTA of greater than 7 days. Individuals with a history of TBI were excluded from the control group. Inclusion in the TBI group required a most significant TBI of mild to moderate severity at the age of 18 years or older. All participants provided written informed consent, and all procedures were approved by the local VA institutional review board.

Materials and procedure

All participants completed a neurological/psychological history screen for inclusion/exclusion criteria and the abbreviated version of the World Health Organization Quality of Life (WHOQOL-BREF) survey.[21] Participants with TBI were administered a semi-structured clinician-administered interview on TBI history and completed the Neurobehavioral Symptom Inventory (NSI).[22]

WHOQOL-BREF

The WHOQOL-BREF is a 26-item abbreviated version of the original WHOQOL-100[23] that measures self-reported QOL.[24] Respondents rate individual items on a Likert scale from 1 (*very poor*) to 5 (*very good*). Twenty-four of the items can be categorized into 4 domains that measure physical capacity (7 items; eg, How well are you able to get around?), psychological well-being (6 items; eg, How satisfied are you with yourself?), social relationships (3 items; eg, How satisfied are you with your personal relationships?), and relationship to salient features of the environment, such as satisfaction with living conditions and health service access (8 items; eg, How satisfied are you with the conditions of your living place?). Each raw domain score was transformed to a 0 to 100 scale per the manual. The measure has shown excellent validity and reliability in a variety of populations across many countries,[23] including individuals with mild to severe TBI.[15]

Neurobehavioral Symptom Inventory

The NSI is a self-report measure of the level of severity of 22 postconcussive symptoms.[22] Respondents are instructed to "rate the following symptoms with regard to how much they have disturbed you *since your injury*" on a 5-point Likert scale (0 = none-rarely if ever present/not a problem at all; 1 = mild-occasionally present, but it does not disrupt activities/I can usually continue what I'm doing/doesn't really concern me; 3 = severe-frequently present and disrupts activities/I can only do things that are simple or take little effort/I feel like I need help; 4 = very severe-almost always present and I have been unable to perform at work, school, or home due to this problem/I probably cannot function without help). The NSI demonstrates high internal consistency (total $\alpha = .95$; subscale $\alpha = .88$-.92) and validity in its ability to differentiate Veterans with a TBI history from those without.[25] The NSI items were subgrouped into somatic/sensory (11 items), cognitive (4 items), and affective (7 items) domains based on the Caplan and colleagues[26] factor analytic study with soldiers who sustained a mild to severe TBI. A full listing of symptoms assessed in the NSI, categorized according to the Caplan et al[26] suggested symptom groupings, can be found in Table 2.

Statistical analyses

Differences in gender and combat exposure distribution between groups were analyzed with a Fisher exact test, due to the small sample size of the control group. Wilcoxon rank sum tests were used to examine differences in age and education between the TBI and control groups as well as the association between QOL and dichotomous sample characteristics (LOC [yes/no], PTA [yes/no], gender [male/female], TBI severity [mild/moderate] and type [blast/blunt]). A

TABLE 2 *Correlations between NSI items and WHOQOL-BREF domains*[a]

NSI item	WHOQOL-BREF domains: Physical	Psychological	Social	Environmental
Somatic/sensory				
Dizziness	−0.14	−0.14	−0.13	−0.19
Balance	−0.31[b]	−0.25[b]	−0.29[b]	−0.14
Coordination	−0.39[c]	−0.38[c]	−0.28[b]	−0.17
Nausea	−0.13	−0.09	−0.18	−0.22
Vision	−0.37[c]	−0.26[b]	−0.28[b]	−0.37[c]
Light sensitivity	−0.38[c]	−0.20	−0.29[b]	−0.35[c]
Hearing	−0.24	−0.15	−0.13	−0.23
Noise sensitivity	−0.05	−0.07	−0.20	−0.08
Numbness/tingling	−0.20	−0.25	−0.16	−0.24
Taste/smell	−0.34[c]	−0.26[b]	−0.09	−0.34[c]
Appetite changes	−0.38[c]	**−0.43**[d]	−0.31[c]	**−0.41**[d]
Cognitive				
Poor attention	−0.40[c]	−0.32[c]	−0.26[b]	−0.33[c]
Forgetfulness	−0.26[b]	−0.15	−0.16	−0.25[b]
Decision making	**−0.42**[d]	−0.37[c]	−0.33[c]	**−0.40**[d]
Organization, slowness	−0.32[c]	−0.22	−0.25[b]	−0.33[c]
Affective				
Headaches	**−0.41**[d]	−0.17	−0.24	−0.22
Fatigue	**−0.41**[d]	**−0.45**[d]	**−0.51**[d]	**−0.41**[d]
Sleep difficulty	**−0.44**[d]	−0.25[b]	−0.35[c]	−0.21
Anxiety	−0.27[b]	−0.23	−0.35[c]	−0.36[c]
Depression	**−0.43**[d]	**−0.46**[d]	**−0.46**[d]	**−0.46**[d]
Irritability	−0.28[b]	−0.34[c]	**−0.47**[d]	−0.34[c]
Frustration	−0.25[b]	−0.15	−0.22	−0.23[b]

Abbreviation: NSI, Neurobehavioral Symptom Inventory.
[a]Bolded numbers represent significance at a Bonferroni-corrected P value .001 or less.
[b]$P \leq .05$.
[c]$P \leq .01$.
[d]$P \leq .001$.

multivariate analysis of covariance, with gender serving as the covariate (due to the univariate differences between groups on gender), was used to assess the differences in the 4 QOL domains between groups.

Within the TBI group, Spearman rank correlation coefficients were used to examine the relationship between continuous variable sample characteristics and QOL, as well as between WHOQOL-BREF and the domains and individual items (ie, symptoms) on the NSI. To assess the contribution of affective, cognitive, and physical postconcussive symptoms on QOL, multiple linear regressions using backward elimination were fitted with total scores of each of the 4 QOL domains serving as the dependent variable and the 3 NSI subscale scores serving as predictors. Additional multiple linear regressions with backward elimination were performed to identify specific symptom predictors for each of the four QOL domains by entering significant symptoms identified through correlational analyses. To avoid overcorrecting for type I errors, while accounting for type II errors, variables were considered significant based on an α level of .001 or less in the correlation analyses. For the multiple regression analyses, we interpreted significance at α alpha level of less than .05 and presented trend findings ($P < .10$) within the final models (see Table 3).

RESULTS

Group differences in demographic characteristics and QOL

The TBI and Veteran control groups did not differ in age, education, or combat exposure; however, the TBI group had a higher proportion of men than the control group (see Table 1), and although not statistically significant, there was notable 20% difference between groups on combat exposure.

Controlling for gender, the multivariate analysis of covariance revealed significant differences between groups on the 4 QOL domains (Wilks $\Lambda = 0.83$, $F_{4,76} = 3.94$, $P = .006$)–Physical QOL: mean (SD) TBI = 49.21 (12.28), controls = 59.38 (10.85)], $F_{1,79} = 12.64$, $P = .001$; Psychological QOL: mean (SD) TBI = 52.64 (14.84); controls = 66.48 (15.04), $F_{12,79} = 13.55$, $P < .001$; Social QOL: mean (SD) TBI = 54.02 (26.68), controls = 73.81 (21.25), $F_{1,79} = 8.17$, $P = .005$; and Environmental QOL: mean (SD) TBI = 61.61 (19.36), controls = 76.0 (18.68)], $F_{1,79} = 6.59$, $P = .012$, indicating that participants with a history of TBI reported worse QOL in all areas than that reported by the control group (see Figure 1).

Predictors of QOL following TBI

Age, education, time since most significant TBI, and the number of traumatic brain injuries were not significantly associated with the 4 domains of QOL in the TBI sample (all P values >.26). Gender, LOC, PTA, TBI severity, and TBI type (blast vs blunt) were also not significantly associated with QOL. Multiple linear regression analyses with the 3 NSI domains serving as predictors of QOL domains revealed that only the Affective NSI domain remained significant in the final models for Physical ($\beta = -.497$, $P < .001$), Psychological ($\beta = -.381$, $P = .003$), Social ($\beta = -.531$, $P < .001$), and Environmental ($\beta = -.455$, $P < .001$) QOL in the TBI sample.

TABLE 3 *Multiple linear regression results for the final models of the 4 WHOQOL-BREF domains[a]*

WHOQOL-BREF domains	R^2	F	P	B	SEB	β	P
Physical	0.278	11.17	**.000**				
Sleep Difficulty (NSI)				−3.50	1.14	−.379	**.003**
Depression (NSI)				−2.40	1.23	−.241	*.055*
Psychological	0.266	10.51	**.000**				
Depression (NSI)				−4.00	1.59	−.330	**.015**
Fatigue (NSI)				−3.27	1.66	−.260	*.054*
Social	0.366	16.71	**.000**				
Fatigue (NSI)				−9.47	2.78	−.418	**.001**
Depression (NSI)				−5.84	2.66	−.269	**.032**
Environmental	0.279	11.23	**.000**				
Depression (NSI)				−5.37	2.06	−.341	**.012**
Fatigue (NSI)				−4.31	2.15	−.263	**.049**

Abbreviations: β, standardized coefficient; *B*, estimated coefficient; NSI, Neurobehavioral Symptom Inventory; SEB, estimated standard error of coefficient B.

[a]Bolded numbers represent significance at a corrected *P* value less than .05; italicized numbers represent trend significant at *P* value less than .10.

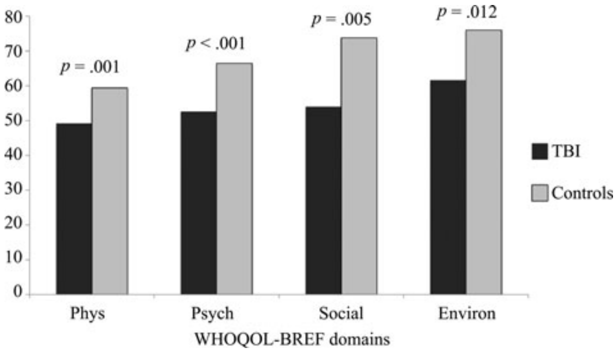

Figure 1. WHOQOL-BREF 0 to 100 transformed scale score means for patients with traumatic brain injury and controls. Higher scores indicate better QOL. *P* values show gender-adjusted multivariate analysis of variance group differences. QOL indicates quality of life; Phys, physical; Psych, Psychological; Environ, Environmental.

Relationships between specific QOL and postconcussive symptoms in TBI

To examine the relationship between specific postconcussive symptoms and areas of QOL, correlational analyses were performed (Table 2). Only interpreting those correlations that met the Bonferroni correction for 88 correlations at the α level of .05 ($P \leq .001$), worse Physical QOL was significantly associated with fatigue, depression, sleep difficulties, headaches, and difficulty with decision making. Poorer Psychological QOL and Environmental QOL were significantly associated with fatigue, depression, and appetite changes. Worse Social QOL was associated with greater fatigue, depression, and irritability.

Multiple linear regression analyses, in which the aforementioned significant symptoms for each of the 4 QOL domains served as predictors, indicated that sleep difficulty best predicted difficulties with Physical QOL whereas depression showed a trend toward significance. Depression best predicted Psychological QOL, with fatigue exhibiting trend toward significance. Both depression and fatigue best predicted Social QOL and Environmental QOL (Table 3).

DISCUSSION

Consistent with previous studies,[11] our results revealed that Veterans with mild to moderate TBI in the post–acute recovery period report worse QOL than demographically matched Veteran control participants. Furthermore, worse Physical, Psychological, Social, and Environmental QOL were moderately associated with greater levels of physical/somatic, cognitive, and affective postconcussive symptoms, with affective symptoms playing a predominant role. Quality of life was unrelated to any of the demographic characteristics, such as age and education, or TBI injury severity markers, including LOC, PTA, time since injury, and number of injuries, in this Veteran sample.

Examination of the relationship between individual symptoms and QOL revealed a somewhat different pattern of symptoms for each QOL domain. One consistent finding was the moderate to strong associations of fatigue and depression with all 4 areas of QOL (Table 2). In assessing which symptoms best predicted specific areas of QOL through multivariate analysis, 3 symptoms emerged as the most relevant to QOL: depression, fatigue, and sleep quality. Overall, depression and fatigue were the most relevant symptoms to QOL in this TBI sample, as they best predicted 3 of the 4 QOL domains (Psychological, Social, and Environmental). Sleep quality emerged as the best predictor of Physical QOL, with depression showing a trend toward significance.

The ubiquitous relationship between mood and QOL was not unexpected, as several studies suggest that there is a strong link between depression and QOL in TBI. Hart and colleagues[16] found that life satisfaction was significantly decreased in individuals with mild to severe TBI and depression compared with TBI individuals without depression. Likewise, Williamson and colleagues[17] found that depression was a significant predictor and mediator of QOL in a mixed (mild to severe) severity TBI sample. It should be noted that in these studies, depression was defined using a comprehensive set of criteria, including several symptoms such as fatigue and attention problems, which were analyzed separately in this study to delineate the relationship between specific symptoms and QOL. Our findings revealed that "feeling depressed/sad," as a singular concept, was still one of the strongest predictors of QOL.

A possible previously underappreciated finding was the strong association between QOL and fatigue. Fatigue has been noted as one of the most common and distressing symptoms endorsed by individuals with TBI.[4,27] Although fatigue is present in 14% to 22% of the general population, estimates for individuals with TBI range from 21% to as high as 77%.[28,29] Consistent with our current findings, a strong association between QOL and fatigue was found in a study of mixed post–acute (>12 months) TBI.[18] Our results suggest that, of all of the postconcussive symptoms assessed, fatigue may be one of the most important symptoms in relation to QOL in mild-moderate post–acute TBI. Fatigue is a multidimensional construct; thus, examination of the relationship between QOL in TBI and fatigue subtypes, such as physical and cognitive fatigue,[30] may advance our knowledge in this area.

Contrary to expectations, fatigue was not independently associated with Physical QOL. Rather, sleep difficulty emerged as an independent predictor of Physical QOL, suggesting that work capacity, mobility, and activities of daily living may be impacted by problems with sleep independent of subsequent fatigue. Although often used interchangeably, "fatigue," "insomnia," and "sleepiness" are recognized as distinct phenomena.[31] It is possible that Physical QOL is more susceptible to "sleepiness" and/or "insomnia" whereas other QOL areas may be more impacted by fatigue. However, as "sleepiness" and "insomnia" were not specifically measured in this study, future research is needed to explore this possibility. It is also possible that sleep problems, fatigue, and depression represent a higher-level construct such as "psychological distress" or "major depression" that varies somewhat in symptom presentation across individuals with a history of mild to moderate TBI. Nevertheless, the current findings underscore the importance of assessing fatigue, sleep difficulty, and sleepiness separately, as they can be independent of each other and differentially affect QOL. It is important to note that this study cannot determine directionality; therefore, alternatively, it is possible that a person's preexisting QOL could impact sleep quality or other symptoms.

Although preliminary, the results of this study may have some important clinical implications. Treatment of depression, fatigue, and sleep difficulties–should they prove to be adversely affecting individuals with TBI histories–may provide for the greatest improvements in overall QOL. Alternatively, interventions that improve QOL may ameliorate certain postconcussive symptoms. Future research will be needed to determine whether such interventions could improve QOL or postconcussive symptoms in Veterans with TBI.

Limitations of this study include a relatively small sample size, the lack of information on the extent of physical injury or disability in both groups, neurobehavioral symptoms in the control group, as well as the limited ability to generalize the results of this study to severe TBI populations. As the majority of our sample was composed of mild TBI (88%), generalization to moderate TBI samples is also cautioned. Although not uncommon for studies of this population, TBI characteristics were determined by self-report and could not be verified through a third party or medical records. Future studies that include a larger sample of moderate or severe TBIs, as well as objective or informant-based measures of TBI characteristics and symptoms, could be helpful in extending the findings of this study.

In summary, results of our study revealed that Veterans with mild to moderate post–acute TBI have worse self-reported QOL than demographically matched Veteran control participants. Overall, "affective" postconcussive symptoms demonstrated the strongest associations with QOL, with depression, fatigue, and sleep difficulty emerging as the most significant individual symptom predictors. Depression and fatigue were the best predictors for Psychological, Social, and Environmental QOL, whereas sleep difficulty best predicted Physical QOL. Findings underscore the importance of examining specific neurobehavioral symptoms as they relate to QOL in mild-moderate post–acute TBI and can potentially guide the development of interventions for improving QOL in this population.

REFERENCES

1. Faul M, Xu L, Wald M, Coronado V. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta, GA: Centers for Disease Control and Prevention; 2010.
2. Tanielian T, Jaycox L, eds. *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery*. Santa Monica, CA: RAND Corporation; 2008.
3. Haboubi NH, Long J, Koshy M, Ward AB. Short-term sequelae of minor head injury (6 years' experience of minor head injury clinic). *Disabil Rehabil.* 2001;23(14):635–638.
4. van der Naalt J, van Zomeren AH, Sluiter WJ, Minderhoud JM. One year outcome in mild to moderate head injury: the predictive value of acute injury characteristics related to complaints and return to work. *J Neurol Neurosurg Psychiatry*. 1999;66(2):207–213.
5. DoD Worldwide Numbers for TBI (2014). http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi. Accessed January 15, 2014.
6. The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1995;41:1403–1409.
7. Dijkers MP. Quality of life after traumatic brain injury: a review of research approaches and findings. *Arch Phys Med Rehabil.* 2004;85(4)(suppl 2):S21–S35.
8. Jacobsson LJ, Westerberg M, Lexell J. Health-related quality-of-life and life satisfaction 6–15 years after traumatic brain injuries in northern Sweden. *Brain Inj*.2010;24(9):1075–1086.
9. Andelic N, Hammergren N, Bautz-Holter E, Sveen U, Brunborg C, Roe C. Functional outcome and health-related quality of life 10 years after moderate to severe traumatic brain injury. *Acta Neurol Scand*. 2009;120(1):16–23.
10. Gross T, Schuepp M, Attenberger C, Pargger H, Amsler F. Outcome in polytraumatized patients with and without brain injury. *Acta Anaesthesiol Scand*. 2012;56(9):1163–1174.
11. Findler M, Cantor J, Haddad L, Gordon W, Ashman T. The reliability and validity of the SF-36 Health Survey Questionnaire for use with individuals with traumatic brain injury. *Brain Inj.* 2001;15(8):715–723.
12. Whiteneck G, Brooks CA, Mellick D, Harrison-Felix C, Terrill MS, Noble K. Population-based estimates of outcomes after hospitalization for traumatic brain injury in Colorado. *Arch Phys Med Rehabil*. 2004;85(4)(suppl 2):S73–S81.
13. von Steinbuechel N, Wilson L, Gibbons H, et al. QOLIBRI overall scale: a brief index of health-related quality of life after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2012;83(11):1041–1047.
14. Emanuelson I, Andersson Holmkvist E, Bjorklund R, Stalhammar D. Quality of life and postconcussion symptoms in adults after

mild traumatic brain injury: a population-based study in western Sweden. *Acta Neurol Scand*. 2003;108(5):332–338.
15. Chiu WT, Huang SJ, Hwang HF, et al. Use of the WHOQOL-BREF for evaluating persons with traumatic brain injury. *J Neurotrauma*. 2006;23(11):1609–1620.
16. Hart T, Brenner L, Clark AN, et al. Major and minor depression after traumatic brain injury. *Arch Phys Med Rehabil*. 2011;92(8):1211–1219.
17. Williamson ML, Elliott TR, Berry JW, Underhill AT, Stavrinos D, Fine PR. Predictors of health-related quality-of-life following traumatic brain injury. *Brain Inj*. 2013;27(9):992–999.
18. Cantor JB, Ashman T, Gordon W, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J Head Trauma Rehabil*. 2008;23(1):41–51.
19. The Management of Concussion/mTBI Working Group. *VA/DoD Clinical Practice Guideline for the Management of Concussion/Mild Traumatic Brain Injury (mTBI): Guideline Summary*. Washington, DC: Department of Veteran Affairs, Department of Defense; 2009.
20. Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA. Clinical evaluation of a measure to assess combat exposure. *Psychol Assess*. 1989;1:53–55.
21. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality-of-life assessment. *Psychol Med.* 1998;28(3):551–558.
22. Cicerone KD, Kalmar K. Persistent postconcussion syndrome: the structure of subjective complaints after mild traumatic brain injury. *J Head Trauma Rehabil.* 1995;10(3):1–17.
23. The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. *Soc Sci Med*. 1998;46(12):1569–1585.
24. Den Oudsten BL, Van Heck GL, De Vries J. Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord.* 2007;22(11):1528–1537.
25. King PR, Donnelly KT, Donnelly JP, et al. Psychometric study of the Neurobehavioral Symptom Inventory. *J Rehabil Res Dev.* 2012;49(6):879–888.
26. Caplan LJ, Ivins B, Poole JH, Vanderploeg R, Jaffee MS, Schwab K. The structure of postconcussive symptoms in 3 US military samples. *J Head Trauma Rehabil*. 2010;25(6):447–458.
27. LaChapelle DL, Finlayson MA. An evaluation of subjective and objective measures of fatigue in patients with brain injury and healthy controls. *Brain Inj.* 1998;12(8):649–659.
28. Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J Head Trauma Rehabil*. 2006;21(3):199–212.
29. Olver JH, Ponsford JL, Curran CA. Outcome following traumatic brain injury: a comparison between 2 and 5 years after injury. *Brain Inj*. 1996;10(11):841–848.
30. Schiehser DM, Delano-Wood L, Jak AJ, et al. Validation of the Modified Fatigue Impact Scale in Veterans with mild to moderate traumatic brain injury [published online ahead of print January 9, 2014]. *J Head Trauma Rehabil*. doi:10.1097/HTR.0000000000000019.
31. Cantor JB, Bushnik T, Cicerone K, et al. Insomnia, fatigue, and sleepiness in the first 2 years after traumatic brain injury: an NIDRR TBI model system module study. *J Head Trauma Rehabil*. 2012;27(6):E1–E14.